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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,348	11/14/2003	Suheir Assady	85189-5400	4072

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EXAMINER	
LIETO, LOUIS D	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 07/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,348	ASSADY ET AL.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-19,26,27 and 34* is/are pending in the application.

4a) Of the above claim(s) *26 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,3-19 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 4/22/2005 is acknowledged. Claims 1, 3-19, 26-27, and 34 are pending in the instant application. Applicant canceled claims 2 and 28-33, and amended claims 1, 3-13 and 15-19. Claims 26-27 remain withdrawn. Claims 1,3-19 and 34 are currently under examination. The sections of title 35 U.S.C not included in this office action can be found in a previous office action. An action on the merits follows.

The rejection of claims 1, 7 and 8 under 35 U.S.C. 101 in the office action of 1/25/2005 is withdrawn because of applicant's amendments to the claims

Priority

Applicant's submission of the amendment to the specification is sufficient to overcome the previous grounds of objection in regards to the failure to include a specific reference to the prior applications.

Claim Rejections - 35 USC § 112

The rejection of claim 17 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reasons of record as presented in the office action of 1/25/2005. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The rejection of claims 28-33 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in view of applicant's cancellation of the claims.

Response to Arguments

Applicant traverses the rejection of claim 17. Applicant first argues that the reference of Halverson et al. is inappropriate because it describes problems with unchecked senescence in adult β cells rather than in hESCs. This point is recognized but it is not considered to be the pivotal factor that applicant suggests. The core of the rejection is the lack of guidance on the specification on existence of insulin producing cell derived from hESCs that over express hTERT and have decreased senescence, and the lack of guidance in the art of record at the time of filing. As set forth in the previous action, Halverson et al. indicates that senescence in some cell types, such as β-islet cells, may be driven by factors other than telomere shortening. Halverson et al. teaches that transduction of human β-cells with hTERT was not sufficient to prevent growth arrest after 10-15 cell divisions, which was similar to untransfected β-cells {Halverson et al. (2000) J. of Endocrinology. 166:103-109; pg 107, col. 1}. Halverson et al. indicates that senescence in some cell types, such as β-islets and human keratinocytes, may be driven by factors other than telomerase shortening (pg. 108, col. 1, pgph 2). Applicant has not provided evidence to support their argument that overexpression of hTERT in differentiated β-cells, even cells derived from hTERT transfected hESCs, can reduce senescence. As of the effective filing date of the claimed invention, the technique of immortalizing or decreasing the senescence of β cells by overexpressing hTERT, regardless of when during differentiation they were transformed with a vector encoding hTERT, would not have been predicted to have such an

effect by the skilled artisan. The specification does not provide any evidence indicating that hESCs overexpressing hTERT would not behave similarly to the cells described by Halverson, as the hESCs differentiated into adult insulin producing cells.

Applicant cites the references of Zalman et al., Wege et al. and WO 03/066839, filed by the instant applicants, Skorecki and Tzuckman, in support of their argument of enablement for claim 17. However all three references represent art that was published post-filing, and well after the claimed priority date of the instant application. As stated in In re Glass, 181 USPQ 31, (CCPA 1974), if a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while the application is still pending by later publications which add to the knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention. Instead, sufficiency must be judged as of the filing date. Further, both Zalman et al., Wege et al. disclose methods of transfecting liver cells, which are distinctly different from totipotent hESCs. Even the fetal progenitor liver cells disclosed by Zalzman et al. represent a developmentally different cell type than the totipotent hESCs of the instant invention. Liver cells, both terminally differentiated and pluripotent are different then totipotent hESCs. Further, Zalman teaches the additional step of transfecting the liver cells with the Pdx1 gene. This step is not contemplated or disclosed in the instant application. Further, WO 03/066839 also fails to disclose that insulin-producing cells, such as β-cells derived from hESCs transfected with hTERT immortalizes them or decreases the senescence of β cells by the overexpression of hTERT. It is again noted that the basis of the enablement rejection is not the unpredictability of transfecting hESCs with hTERT. Instead the issue is the lack of predictability that said transfection would reduce senescence of insulin producing cells derived from the hESCs, such as

β-cells. Based on the state of the art at the time of filing the skilled practitioner would not have predicted that transforming hESCs with hTERT would have produced insulin producing cells with deceased senescence. Further, the lack of disclosure in the specification on the successful production of the claimed cells would not have enlightened the skilled practitioner on how to successfully make the claimed cells. The rejection is maintained over this issue for reason of record as stated above and in the office action of 1/25/2005.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 2, 5, 6, 8, 12, 13, 14, 15, 16, 28, 30, 31, 33, and 34 are rejected under 35 U.S.C. 102(a) as being anticipated by Lumelsky et al. {Lumelsky et al. (April 26, 2001) Science 292:1389-1394} is withdrawn. Applicant's arguments, see the reply, filed 4/22/05, have been fully considered and are persuasive.

Claims 1,3-16 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Assady et al. {Assady et al. (September 2000). Vol. 11, Program and Abstract Meeting infor: 33rd Annual meeting of the American Society of Nephrology and the 2000 Renal Week Toronto, Ontario. Canada. Abstract (A1956)}. Applicant should note that the authors are exactly the same as the inventors listed on the instant invention. However, since the date of publication of the abstract by Assady et al. is more than a year before the priority date of 10/15/2001, it is properly applied as 102(b) art. Claims 28 and 33 were canceled; therefore the rejection over these claims is withdrawn.

Assady et al. provides guidance on the generation of stable insulin producing β-cells derived from Human Embryonic stem cells (Abstract). Assady et al. teaches that the β-cells are induced to produce insulin in response to exposure with glucose. A cell that produces a protein, such as insulin, inherently expresses the gene that encodes the protein. Further, the term isolated encompasses cells grown in culture, which have been isolated from their native environment. Thus, by teaching all the limitations of the claims as written, Assady et al. anticipates the instant invention as claimed.

It is noted that the enriched or purified preparations of isolated cell populations derived from a human embryonic stem cell line are not distinguishable from those previously known in the art. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934) and MPEP 2112.01.

Response to Arguments

Applicant argues that Assady et al. does not teach, disclose or suggest the isolated cell populations as recited. Applicant states that "the present invention enables the directed differentiation of hESCs to insulin-producing cells and thus enables directed enrichment of hESCs for insulin-producing cells" and that this is not disclosed by Assady et al. Finally, applicant argues that Assady et al. does not disclose or suggest specific genetic modifications of hESCs.

In response it is noted that applicants claims are drawn to a product, an isolated cell population, and not the process of making the product. There is no basis to distinguish applicant's cells from those in the art. Applicant has not shown that any of the cells of Assady et al. are different from the claimed product. Further, while Assady et al. may teach different methods of isolating and deriving the insulin producing cell population, applicant has provided neither arguments nor evidence that the method of isolation or derivation alter the cells isolated. That is, there are neither arguments nor evidence that the methods of Assady et al. would produce cells that do not produce insulin.

Finally, applicant should note that Assady et al. et al was not used as basis of rejection over any claims that are limited to insulin producing cells that have been genetically modified. Therefore this argument is moot. The rejection is maintained over Assady et al. for reason of record as stated above and in the office action of 1/25/2005.

Claims 1,3-16 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Peakman et al. {Peakman et al. (1994) Transplantation 57:384-393}.

Peakman et al. provides guidance on the isolation of insulin producing cells from a human pancreas using collagenase digestion (Abstract; pg. 385, col. 1, Materials and Methods). Further, Peakman et al. teaches the enrichment of a insulin producing cell population by handpicking dithizone-positive islets prior to trypsin and cytospin preparation (pg. 388, col. 2) . Said handpicking of the islets meets the limitations of the term isolated. Peakman et al. teaches that these cell populations are glucose responsive insulin producing cells, which stably secret insulin over a 24 hour period of time (; pg. 385, col. 1, Materials and Methods; pg. 387, pgph 4). "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) Thus, by teaching all the limitations of the claims as written, Peakman et al. anticipates the instant invention as claimed.

It is noted that the enriched or purified preparations of isolated cell populations derived from a human embryonic stem cell line are not distinguishable from those previously known in the art. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658

(Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934) and MPEP 2112.01.

Response to Arguments

Applicant argues that cells taught by Peakman et al. differ from the claimed cell population because they are short-lived. Applicant argues that the claimed cells of the instant application are long-lived and points to paragraph 15 of published application. It is noted that this paragraph is actually drawn to an aspect of the present invention of which a preferred embodiment is that they be long-lived. However, the claims are not limited to long-lived cells, and even if such a limitation was present it is not clear what the frame of reference would be for determining whether a cell was long-lived or short lived. Finally, applicant argues that the instant cell population differs from that of Peakman et al. because they were not obtained by the use of proteolytic enzymes and because the instant cell population comprises β-cell precursors capable of maintaining their pluripotency because they are derived from an hESC line. It is noted that claimed invention encompasses terminally differentiated β-cells as well.

In response it is noted that applicants claims are drawn to a product, an isolated cell population, and not the process of making the product. There is no basis to distinguish applicant's cells from those in the art. Applicant has not shown that any of the cells of Peakman

et al. are different from the claimed product. Further, while Peakman et al. may teach different methods of isolating and deriving the insulin producing cell population, applicant has provided neither arguments nor evidence that the method of isolation or derivation alter the cells isolated from the claimed cell population. That is, there are neither arguments nor evidence that the methods of Peakman et al. would produce cells that do not produce insulin. The rejection is maintained over Peakman et al. for reason of record as stated above and in the office action of 1/25/2005.

Claim Rejections - 35 USC § 103

The rejection of claims 1,3-16 and 34 are under 35 U.S.C. 103(a) as being unpatentable over Soria et al. {Soria et al. (2000) Diabetes 49:1-6} and in view of Chrenek et al. {Chrenek et al. (1998) Theriogenology 50:659-666} is withdrawn. Applicants amendments to the claims and arguments, see the reply, filed 4/22/05, have been fully considered and are persuasive.

Claims 15, 18, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Assady et al. {Assady et al. (September 2000). Vol. 11, Program and Abstract Meeting infor: 33rd Annual meeting of the American Society of Nephrology and the 2000 Renal Week Toronto, Ontario. Canada. Abstract (A1956)} in view of Soria et al. {Soria et al. (2000) Diabetes 49:1-6}.

Assady et al. provides guidance on the generation of stable insulin producing β-cells derived from Human Embryonic stem cells (Abstract). Assady et al. teaches that the β-cells are induced to produce insulin in response to exposure with glucose. A cell that produces a protein, such as insulin, inherently expresses the gene that encodes the protein. Further, the term isolated

encompasses cells grown in culture, which have been isolated from their native environment. Finally, Assady et al. teaches that the cells can be used for cell replacement therapy to treat a patient with a disease such as diabetic nephropathy (Abstract). The use of cells for cell replacement therapy inherently comprises transplanting the cells into a subject. Assady et al. does not teach the transfection of the cells with a construct comprising an insulin promoter

It is noted that the enriched or purified preparations of isolated cell populations derived from a human embryonic stem cell line are not distinguishable from those previously known in the art. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934) and MPEP 2112.01.

Soria et al. provides guidance on derivation of an insulin secreting clone from mouse embryonic stem cells (pg. 1, Abstract, Research Design and Methods). Soria et al. teaches that the insulin secreting clones are selected BY using a neomycin (Neo) selection system, which

involves transfection with a Neo construct under the control of the human insulin promoter (pg. 2, Fig. 1, Col. 2, Results). Soria et al. teaches that the ESC derived insulin secreting cells have *in vitro* regulated insulin release (pg. 2, col. 2, pgph 2; pg. 3, Table 1). Further, Soria et al. teaches that the ESC derived insulin secreting cells maintain a stable *in vivo* glucose response after ectopic implantation into the spleen of mice with experimental diabetes (pg. 3, col. 2, pgph 2; pg. 1, Research Design and Methods). Finally, Soria et al. states that xenotransplantation to restore β-cell function in type 1 or 2 diabetes has multiple problems, such as the technical difficulty, risk of animal retroviral infection, and immunological rejection (pg. 1, col. 2, pgph 2). Soria et al. concludes by stating that a useful "alternative is the use of embryonic stem cells" to produce insulin secreting cells (pg. 1, col. 2, pgph 2).

Based on the guidance provided by Assady et al. on the generation of stable insulin producing β-cells derived from hESCs and the teachings of Soria et al. on the enrichment of insulin producing mESCs using a Neo selection system, it would be *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Assady et al. by transfecting the hESCs with a Neo construct under the control of the human insulin promoter, in order to enrich the cell population for insulin producing cells.

A practitioner in the art would be motivated to enrich a population of insulin-producing cells derived from human ESCs in order to transplant them into humans to treat diabetes and avoid the problems associated with xenotransplantation as taught by Soria et al.

The person of ordinary skill in the art would have a reasonable expectation of success because the transfection of human ESCs instead of mouse ESCs with construct taught by Soria et al. comprises a minor modification of the teachings of Soria et al.

No claims allowed.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-272-0735. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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